REMARKS

The Invention.

The present invention provides fusion polypeptides comprising a signal peptide functional in *Aspergillus*, a secreted polypeptide or portion thereof normally secreted from *Aspergillus*, an optional cleavable linker and a desired glycosyltransferase from which the transmembrane anchor region has been deleted.

Status of the Application.

Claims 11-18 are pending in the application.

Claims 1-10 have been cancelled as drawn to a non-elected invention without prejudice and Applicants reserved the right to file further continuation applications on any subject matter disclosed in the instant application or on the subject matter of any previously or presently cancelled claim.

Claim 11 has been amended to correct a grammatical error. Applicants assert new matter has not been introduced by the amendment.

35 U.S.C. §112, first paragraph.

Claims 11 and 12

Claims 11 and 12 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that Claims 11 and 12 are so broad as to encompass any signal peptide from any source and any secreted polypeptide secreted from *Aspergillus*. Applicant respectfully traverses.

The Examiner alleges that the claims encompass any signal peptide. However, this is an incorrect reading as the claims clearly recite that the signal peptide must be functional in *Aspergillus*. Thus, there is a definite, finite group of signal peptides that will function as secretion signals in *Aspergillus*.

Similarly, he alleges that the claims encompass any polypeptide secreted from *Aspergillus*. Once again Applicants assert that this is an incorrect reading of the claims as currently presented. The claims require that the polypeptide be normally secreted by *Aspergillus*. Thus, only endogenously expressed and secreted proteins by Aspergillus may serve in this role and is not an unlimited number as suggested by the Examiner.

It is settled law that the Patent Office, in asserting an enabling disclosure is not commensurate in scope with the protection sought, must support such assertions with evidence or reasoning substantiating the doubts so expressed. In re Dinh-Nguyen, 181 U.S.P.Q. 46 (CCPA 1974). The Patent Office requirement is further described in In re Bowen, 181 U.S.P.Q. 48 (CCPA 1974):

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112, *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. . . .
>
> Here, the only reason given appellant why his specification does not enable one skilled in the art to use his invention as broadly as it is claimed is the statement of the board that "polymerizable materials" include "not only . . . all of the very many organic polymers . . . but also inorganic polymers." But even this statement only identifies a subgenus of "polymerizable materials" without giving a reason for the implication inherent therein that inorganic polymers would not work in appellant's process. . . .
>
> Accordingly, there appears to be no basis for the non-enablement rejection on the theory that claims read on undisclosed polymers. While the claims literally comprehend numerous polymers in addition to the one specifically described in appellant's specification, nylon 66, no persuasive reason has been given by the Patent Office why the specification does not realistically enable one skilled in the art to practice the invention as broadly as it is claims."

In the present case, the Office Action provides no extrinsic evidence regarding non-enablement. Instead, the Office Action relies upon the opinion of the Examiner that the breadth of the claim is unsupportable because there aren't enough examples. While the Office Action does review the results provided in the Examples and suggests its position

that these results are insufficient, the Office Action is entirely devoid of technical reasoning and/or reference to extrinsic evidence which supports the position therein that one of skill in the art would be unable to make and use the invention as claimed. Accordingly, Applicants respectfully submit that the unsupported opinion of the Examiner that a specific claimed embodiment is "too broad" and would require undue experimentation is not the standard of non-enablement.

Withdrawal of the rejection is respectfully requested.

Claims 11 - 13

Claims 11-13 stand rejected under 35 USC §112, first paragraph as allegedly containing subject which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that the "specification does not contain any disclosure of the structure of all the polypeptide sequences that are encompassed by them." See page 6 of the Office Action. Applicants respectfully traverse.

Applicants note that it is not necessary under §112 that every claimed embodiment be specifically exemplified. Applicants respectfully submit that a skilled artisan would be able to glean from the specification the metes and bounds of the invention. As noted above the number of polypeptides encompassed by the present claims is finite and well within the skill of the ordinary artisan.

Applicants assert that the written description is met and respectfully request withdrawal of the rejections.

35 U.S.C. §112, second paragraph.

Claims 11 and 12-18 stand rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regardas as the invention. Specifically, the Examiner has pointed out that the phrase "amino acid sequence comprising a desired glycosyltransferase from which the transmembrane anchor coding region has been deleted" is incorrect. Applicants have amended Claim 11 to correct the phrase.

Applicants note that the Examiner states that this incorrect phrase appears in "several instances." However, Applicants were able to locate it only once, which has been corrected. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §103.

The Examiner has maintained his rejection of Claims 1-10 under 35 USC §103(a) as being unpatentable over either Lawlis (a) et al. (US Pat. No. 5,679,543) or Lawlis (b) et al. (US Pat. No. 6,130,063) and Kitagawa et al. (BBRC (1994) 194(1):375-382) or Ward et al (Biotechnology (1990) 8:435-440) and Kitagawa et al. Applicants respectfully traverse the rejections.

Initially, Applicant notes that the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit requires that the combination of the teachings of all or any of the references would have suggested the possibility of further improvement by combining such teachings. Thus, the test of whether it would have been obvious to select specific teachings and combine them must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *See* In re Dance, 160 F.3d 1339, 48 USPQ2d 1635 *quoting* In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), and In re Vaeck, 20 USPQ2d 1439 (Fed. Clr. 1991).

Applicants submit that while the Lawlis and Ward *et al.* references teach fusion constructs for the secretion of heterologous proteins in *Aspergillus*, they do not suggest

to the skilled artisan to carry out the presently claimed invention. Furthermore, applicants submit that the references do not provide the skilled artisan with a reasonable expectation of success in so carrying out the presently claimed invention.

Lawlis (a) (US Pat. No. 5,679,543) or Lawlis (b) (US Pat. No. 6,130,063)

Lawlis (a or b) teaches that heterologous proteins may be secreted at enhanced levels as fusion proteins compared to the levels achieved when it is not fused to a *secreted* Aspergillus polypeptide. Lawlis also teaches the stable expression of heterologous proteins via *integration* of the plasmids. See column 16, lines 59 et seq. However, Lawlis fails to describe a fusion polypeptide that is encompassed by the presently amended claims. It fails to teach or suggest that: 1) a normally membrane-bound enzyme such as a glycosyltransferase can be secreted, 2) the cleavable linker is optional, and 3) a truncated gene is suitable for expression in an integration plasmid.

Ward et al (Biotechnology (1990) 8:435-440)

Ward *et al.*, like Lawlis above, is concerned with the improvement in the secretion of a normally secreted enzyme, chymosin. There is nothing in Ward *et al.* that teaches or suggests that a normally membrane-bound enzyme can be secreted if produced as a fusion polypeptide or that truncated gene is suitable for expression in an integration plasmid.

Furthermore, Ward *et al.*, notes that not only are there differences in the expression and secretion levels of various constructs within a single host organism but also that similar constructs give different results in different organisms. See page 435, last full paragraph. This supports Applicants' position that one skilled in the art would not have a reasonable expectation of success in transferring one expression construct from one host system to another OR that alterations in an expression construct, e.g., using a truncated gene instead of a full-length gene, would work.

The expression properties of a fungus are much more likely to resemble those of another fungus than a bacterial or mammalian host cell. Yet there were no reports of

successful expression and secretion of glucosyltransferases in fungi or yeast prior to the Applicants work.

Kitagawa et al. (BBRC (1994) 194(1):375-382)

Kitagawa *et al.* does not teach or suggest that other expression systems could be used to express glycosyltransferases generally or that the expression constructs used in their studies could be transferred to other host cells. It is well known in the art that one cannot transfer the expression/secretion results from one host to another with a reasonable expectation of success.

In addition, Kitagawa *et al.* does not teach or suggest: 1) a secretion signal functional in *Aspergillus*; 2) a secreted polypeptide or portion thereof which is normally secreted from a filamentous fungus, and particularly from *Aspergillus*; or 3) optionally a cleavable linker polypeptide.

Kitagawa *et al.* uses a mammalian insulin secretion signal (i.e., dog; see Quesenberry, M. S. and Drickamer, K. (1991) Glycobiology 1, 615–621) and a Protein A IgG binding domain linked to the glycosyltransferase. Protein A is not a secreted protein even from its native host; it is a membrane bound protein. Furthermore, the protein A isn't for enhancing the expression and secretion of the heterologous protein; it is for ease in purification.

Applicants therefore submit that the Kitagawa disclosure is limited to two significant areas: 1) the expression vector used was for mammalian systems; and 2) the expression vector was not designed to provide stable expression, i.e., it is for transient expression. See Kitagawa and references 6 and 7 cited by Kitagawa (attached). There is absolutely no suggestion of the use of the vector for commercial quantities of the enzyme in a fungal host or expression system. Thus, taken as a whole, as the Examiner is required to do[1], one of skill in the art would read the Kitagawa reference as teaching the use of a specific vector in a mammalian expression systems, not for the purpose of producing commercial quantities of the enzyme *per se* but rather

[1] The Federal Circuit has determined that it is not legally proper to focus on individual substitutions and differences instead of on the invention *as a whole*. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 USPQ 81 (Fed.Cir. 1986), *cert. den.*, 480 U.S. 947, 107 S.Ct. 1606 (1987).

for the production of minute quantities. Thus, one of skill in the art would view Kitagawa et al. as teaching away from the present invention, i.e., only minute quantities would be produced with this construct. Motivation to move to a new expression system to produce commercial quantities is simply lacking.

A *prima facie* case of obviousness requires the Examiner to cite to a reference or a combination of references which (a) suggests or motivates one of skill in the art to modify the teachings of the reference(s) to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims at issue. *See e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness as discussed below.

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the references to arrive at the **claimed invention.** *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

None of the references contain a suggestion or teaching that they should be combined in a way that results in the present invention. In fact, as noted elsewhere herein, there are numerous teachings away from the present invention.

The Examiner asserts that Lawlis (a or b) teaches the "production of any protein irrespective of the fact whether it is normally bound or not." Applicants respectfully disagree. Lawlis teaches that the desired polypeptides "include mammalian enzymes

such as bovine chymosin, human tissue plasminogen activator etc., mammalian hormones such as human growth hormone, human interferon, human interleukin and mammalian proteins such as human serum albumin. Desired polypeptides also include bacterial enzymes such as α-amylase from Bacillus species, lipase from Pseudomonas species, etc. Desired polypeptides further include fungal enzymes such as lignin peroxidase and Mn^{2+}-dependent peroxidase from Phanerochaete, glucoamylase from Humicola species and aspartyl proteases from Mucor species." It should be noted that these are all intact, mature secreted proteins and that Lawlis is particularly interested in the production of chymosin. There is no mention that truncated proteins will work in the system. Thus, Lawlis fails to suggest that a truncated protein would be a "desired polypeptide."

As for Ward *et al.*, Applicants would like to point out that the teachings of Ward *et al.* are essentially the same as for Lawlis and, thus, the arguments presented above for Lawlis also apply to Ward *et al.* Further, the Examiner admits (and agrees with the Applicants) that this reference does NOT teach "that a normally membrane-bound enzyme can be secreted if produced as a fusion protein." However, the Examiner believes, erroneously, that the Applicants bear the burden of proof that the truncated enzyme would work because "the reference does not at the same time teach that normally membrane-bound proteins cannot be used for production." See page 8 of the Office Action. First, the burden of proof is on the Examiner to provide a reasoned argument why a skilled artisan would choose one teaching over another. See *supra*. The Examiner's unsupported opinions cannot serve as the basis for an obviousness rejection.

Turning now to Kitagawa *et al.*, the Examiner asserts that this reference teaches "the cloning and expression of a polynucleotide encoding a human sialyltransferase lacking the signal-anchor (i.e., membrane anchor) sequences (the first 60 amino acids) as [a] fusion protein comprising the human insulin signal sequence in the place of the signal-anchor peptide in the instant invention and comprising protein A in place of the secreted Aspergillus polypeptide in the instant invention." The Examiner further asserts that "availability of a normally membrane bound glycosyltransferase in a soluble form" is

provided by the Kitagawa *et al.* reference. Although this may be correct the Examiner has ignored the fact that the transfer of an expression cassette useful in one host system is not transferable to another, different, host system. There is no teaching in Kitagawa *et al.* that the truncated gene if fused to another protein or fragment thereof with yet another different signal sequence in yet another host system that it would function properly. It is just as likely, if not more so, that the only reason there the secretion of an active enzyme is due to the presence of the protein A in the construct and that without that sequence then proper folding of the enzyme would not have occurred. In other words, there is no reason to believe that the truncated sialyltransferase would possess activity if fused to another protein. In addition, there is no reason why a skilled artisan would use the truncated gene without the other elements of the mammalian expression construct for use in a fungal expression construct. The Examiner's assertions simply are conjecture and a matter of opinion without the necessary support for a finding of obviousness.

Finally, a fundamental requisite of establishing a *prima facie* case of obviousness is that there is a reasonable expectation of success in practicing the recited method steps or producing the claimed composition, without the use of the pending Application. Indeed,

> "[t]he reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

The reasonable expectation of success must be founded in the prior art, not Applicant's disclosure, and in view of the prior art's lack of correlation between mammalian and fungal expression systems, no logical argument can be advanced in support of the cited reference's teaching of a reasonable expectation of success based on either Lawlis (a) *et al.* (US Pat. No. 5,679,543) or Lawlis (b) *et al.* (US Pat. No. 6,130,063) and Kitagawa *et al.* (BBRC (1994) 194(1):375-382) or Ward *et al.* (Biotechnology (1990) 8:435-440) and Kitagawa *et al.* Certainly there is no motivation to combine the references as suggested by the Examiner or by the references themselves. The modification failed to possess the requisite expectation of success.

The Examiner asserts that "Expression of ... a sialyltransferase by Kitagawa et al. provides a reasonable expectation of successful expression using the system provided by Lawlis." See Office Action, page 5. In addition, the Examiner asserts that "a reasonable expectation of success because Ward et al. provide methods from making such a polynucleotide in general and Kitagawa et al. provide a similar method but less robust than the method of Ward et al." Applicants respectfully disagree. The Examiner's statements are unsupported opinions and are contrary to the teachings of the prior art.

The selection of the combination suggested by the Examiner is not fairly suggested in the prior art. The Examiner impermissibly picks and chooses ingredients without considering the invention as a whole, and looks suspiciously like hindsight reconstruction reached through the teachings of Applicants' disclosure. At best, the analysis is obvious to try.

Applicants further respectfully assert that by suggesting that Kitagawa reference teaches the use of a truncated glycosyltransferase nucleotide vector, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 [Fed. Cir. 1988], *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 [Fed. Cir. 1989]).

Withdrawal of the rejections is respectfully requested.

Double Patenting

The Examiner has rejected Claims 1-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-8, 11, 13, 14 and 16 of Lawlis (a) *et al.* (US Pat. No. 5,679,543) or Claims 1-8, 11, 13, 14 and 16 of Lawlis (b) *et al.* (US Pat. No. 6,130,063) and in view of Kitagawa *et al.* (BBRC (1994) 194(1):375-382).

Applicants believe for the reasons stated above that the present claims are not obvious over the cited art. However, Applicants respectfully request that the double patenting rejection be held in abeyance until there is agreed upon patentable subject matter in the present application, and then, if appropriate, Applicants would be willing to file a terminal disclaimer. The Examiner is hereby requested to allow this Response to be fully responsive to the Office Action mailed July 25, 2003.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,
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